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CORRESPONDENCE

Encephalitis in the Setting of COVID-19 Infection

To the Editor—In their article "Clinical Presentation and Outcomes of Severe Acute Respiratory Syndrome Coronavirus 2–Related Encephalitis," Pilotto and colleagues reported on the incidence of encephalitis in a multicenter cohort of coronavirus disease 2019 (COVID-19) patients [1]. The reported incidence of 50 per 100 000 may be overestimated. Their definition of encephalitis corresponds to the designation of "possible encephalitis" as proposed by Venkatesan et al in their 2013 consensus article [2]. The diagnosis of probable encephalitis requires presentation with altered mental status (AMS) and at least 3 minor criteria relating to cerebrospinal fluid (CSF) pleocytosis, magnetic resonance imaging (MRI) changes, electroencephalogram changes, new-onset seizures, or focal neurologic deficits [2]. The diagnosis of confirmed encephalitis further requires pathological confirmation or laboratory evidence of a causative organism or highly clinically relevant neuronal autoantibody. The definition used by Pilotto et al (AMS and 2 minor criteria) allows for overestimation of encephalitis. In fact, 8 of their 25 patients (32%) had unremarkable brain MRI and CSF. The diagnosis of encephalitis in those 8 patients was based solely on the clinical picture, which makes the diagnosis questionable at best. Generalized seizures and AMS can occur in the setting of viral sepsis or metabolic derangements associated with COVID-19 infection [3]. They should not be utilized as evidence of encephalitis in this setting. In addition, aphasia and dysarthria are difficult to ascertain in the setting of AMS and should not be considered as focal deficits in altered patients. The fact that nearly half the patients were not tested for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) in the CSF or for neuronal autoantibodies adds to the limitations of this study by allowing significant misclassification of infectious versus parainfectious versus autoimmune etiologies. The authors concluded that most cases of COVID-19–related encephalitis were parainfectious in nature, secondary to the associated cytokine storm. This claim cannot be made if half the patients were not tested for SARS-CoV-2 PCR in the CSF nor for neuronal autoantibodies in both the serum and CSF. Moreover, the authors did not report on cancer screening in their cohort, possibly missing patients with an incidental paraneoplastic etiology, a major cause of encephalitis [4]. With modern epidemiological data suggesting that autoimmune encephalitis may be as common as viral encephalitis [5], scientific reports addressing encephalitis related to COVID-19 (or any cause) should adhere to certain reporting standards to avoid etiological misclassification. At a minimum, all patients should be tested for common microbiological pathogens of encephalitis as well as clinically relevant neuronal autoantibodies [6]. Patients without evidence of direct CNS infection should undergo cancer screening to rule out paraneoplastic etiologies. Administering unnecessary immunomodulating therapies to encephalopathic patients with COVID-19 can have negative effects, especially in cases complicated by secondary bacterial infections. In addition, overestimating the incidence of COVID-19–related encephalitis may result in missing important alternative causes of encephalitis (eg, cancer or antibody mediated) if full encephalitis workup is not pursued in each case.

Notes

Potential conflicts of interests. H. A. is a consultant for Biogen, Genentech, Celgene, Alexion, and Viela Bio; and receives research support to conduct clinical trials from Genentech, Novartis, and Celgene. The author has submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Hesham Abboud

Multiple Sclerosis and Neuroimmunology Program, University Hospitals of Cleveland, Case Western Reserve University, Cleveland, Ohio, USA

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Correspondence: Hesham Abboud, MD, PhD, University Hospitals, Cleveland Medical Center, Bolwell, 5th floor, 11100 Euclid Avenue, Cleveland, OH 44106 (Hesham.abboud@uhhospitals.org).

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